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LEUKAEMIA IN CHILDHOOD AND YOUNG ADULT LIFE

TRENDS IN MORTALITY IN RELATION TO AETIOLOGY

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There is good reason to believe that the different clinical and cytological types of leukaemia represent distinct diseases. Thus there are major differences between the age and sex distributions of chronic lymphatic, chronic myeloid, and acute leukaemia (MacMahon and Clark, 1956). Furthermore, ionizing radiations have been shown to cause chronic myeloid and acute leukaemia, but they have not been shown to cause chronic lymphatic leukaemia, and the geographical distribution of the first two types differs from that of the last in that chronic lymphatic leukaemia is relatively rare in the Far East (Wells and Lau, 1960). Finally, recent cytogenetic data have demonstrated the existence of a specific chromosomal abnormality in many cases of chronic myeloid leukaemia, but, so far, not in any other type of leukaemia (Nowell and Hungerford, 1960; Baikie, Court Brown, Buckton, Harnden, Jacobs, and Tough, 1960). Clearly, therefore, the various types of leukaemia should be separated in any study of its aetiology. Until recently this has been possible only in studies based on hospital data. Insufficient details have been published in the national vital statistics for mortality of the various types to be examined separately; moreover, many of the deaths attributed to leukaemia have been certified as due to leukaemia without further specification.

An opportunity to make a more detailed examination of the trends in mortality was provided by the British Registrars-General when they extracted information from the records of all persons certified as dying from leukaemia since 1945 and made it available to the Medical Research Council. This information can be used to re-classify the causes of death in any desired way. The results obtained for adults aged 15 years and over in England and Wales have been published previously (Court Brown and Doll, 1959). The present paper contains similar data for children and for young adults under the age of 30 years. Data for young adults have been included because the mortality from leukaemia is at a minimum between the ages of 20 and 29 years, and this age period provides a natural break between the childhood and adult forms of the disease. Moreover, Lee (1961) has shown that there is a small peak in the mortality from leukaemia at ages 15–19 years, and this is missed if the break is made earlier.

The total leukaemia mortality at these ages in England and Wales has also been examined over a longer period, and some of the data are compared with similar data from other countries.

Results

The mortality from leukaemia in childhood and early adult life varies sharply with age. The extent of the variation is illustrated in Fig. 1, which shows the age-specific death rates for England and Wales for the period 1945–59. A sharp peak in mortality is seen to occur at age 3 years in both sexes, and a smaller peak is shown at ages 15–19 years in males. It seems possible that different factors may be responsible for the production of these peaks, so that it is desirable to examine the mortality in the principal age-groups separately.

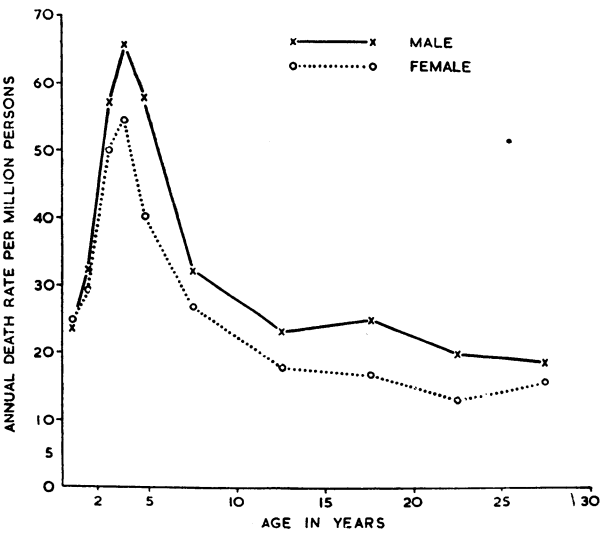

FIG. 1.—Age-specific death rates from leukaemia under the age of 30 years by sex in England and Wales, 1945–59.

Mortality from Different Types of Leukaemia

The deaths recorded during the five-year periods 1945–9, 1950–4, and 1955–9 were classified into nine diagnostic categories: (1) acute lymphatic leukaemia;

(2) chronic lymphatic leukaemia ; (3) lymphatic leukaemia of unspecified type ; (4) acute myeloid leukaemia ; (5) chronic myeloid leukaemia ; (6) myeloid leukaemia of unspecified type ; (7) other and unspecified acute leukaemias ; (8) unspecified chronic leukaemias ; and (9) leukaemia without further description. At ages under 30 years, and especially in childhood, chronic leukaemia is extremely rare, and the great majority of the cases described merely as "lymphatic" or "myeloid" leukaemia are likely to have been cases of acute leukaemia. The original nine groups were therefore reduced by combining the data for (*a*) acute and unspecified lymphatic leukaemia and (*b*) acute and unspecified myeloid leukaemia. Similarly it was assumed that unspecified leukaemias were also acute, and they were added to the group of unspecified acute leukaemias.

Finally, the few cases of unspecified chronic leukaemia were allocated to the groups of chronic lymphatic leukaemia and chronic myeloid leukaemia in proportion to the numbers of cases given these specific diagnoses in the corresponding quinquennia and five-year age-groups. By this means mortality rates could be estimated for five types of leukaemia—acute lymphatic, chronic lymphatic, acute myeloid, chronic myeloid, and other and unspecified acute leukaemia. Whether it is useful to separate the acute leukaemias in this way is uncertain. The diagnosis of the various types of acute leukaemia may be extremely difficult, and even after detailed examination by expert haematologists it may be impossible to obtain agreement over the proper classification of a particular case. The description of the type of leukaemia given on a death certificate will not necessarily be based on an expert opinion, and it must be presumed that many of the descriptions are erroneous. Nevertheless, there is evidence of sharp variation in the proportion of the different types of acute leukaemia diagnosed at different ages in childhood and early adult life, and it seems probable that the trends reflect real differences, even though the classification of individual cases may be inaccurate.

The results obtained for the period 1945 to 1959 are shown in Table I and Fig. 2. For acute lymphatic leukaemia the maximum mortality was recorded in the fourth year of life in both sexes. Among boys the mortality rose to more than four times that recorded in the first year of life (7.9 to 33.5 per million) ; among girls it rose more than three times (9.3 to 29.8 per million). At older ages the mortality fell rapidly, with only a slight check at ages 15 to 19 years. The lowest figure recorded (at ages 25–29 years) was less than half that recorded in the first year. The mortality attributed to acute myeloid leukaemia showed less variation. Among males the mortality varied from 100 to 225% of that recorded in the first year ; among females the mortality ranged from 88 to 148%. In both sexes the maximum rate was recorded between ages 2 and 4 years, but there was also a secondary peak, more pronounced in males than females, at ages 15 to 19 years. In view of the inaccuracy of a classification limited to death-certificate data, it is possible that the childhood peak in mortality from acute myeloid leukaemia and the check in the rate of fall of the mortality from acute lymphatic leukaemia in late adolescence are artifacts due to misclassification.

The mortality from chronic leukaemia remained low within the age limits studied, and the variations other than the increase attributed to chronic myeloid leukaemia above the age of 20 years may well be due to misclassification.*

TABLE I.—*Mortality from Leukaemia in England and Wales, 1945–59, Divided by Sex, Age (0 to 29 Years), and Type of Leukaemia*

Sex	Age (Years)	Annual Leukaemia Death Rate per Million					
		Acute Lymphatic	Acute Myeloid	Other and Unspecified Acute	Chronic Lymphatic	Chronic Myeloid	All Types
Male	0	7·9	5·1	11·0	0·2	0·2	24·4
	1	12·5	8·2	11·2	0·2	0·2	32·3
	2	31·5	9·8	14·4	0·9	0·9	57·4
	3	33·5	11·5	17·8	2·1	0·8	65·7
	4	30·9	11·5	14·4	0·4	0·6	57·8
	5–9	15·4	6·0	9·6	0·4	0·4	31·8
	10–14	9·9	6·9	5·6	0·4	0·4	23·3
	15–19	8·8	9·4	6·7	0·2	0·5	25·5
	20–24	6·0	7·6	5·5	0·3	1·0	20·4
	25–29	3·9	8·1	4·4	0·3	2·1	18·8
Female	0	9·3	5·6	10·8	0·0	0·0	25·7
	1	13·3	6·1	9·6	0·4	0·4	29·8
	2	25·6	8·3	14·5	0·5	0·5	49·4
	3	29·8	7·2	16·3	0·7	0·5	54·5
	4	23·2	4·9	11·6	0·4	0·0	40·2
	5–9	12·7	6·2	7·6	0·3	0·2	27·0
	10–14	6·2	6·7	4·4	0·1	0·3	17·7
	15–19	5·0	6·9	4·6	0·0	0·5	16·9
	20–24	3·3	5·4	4·1	0·1	0·9	13·8
	25–29	3·1	6·4	4·4	0·3	1·8	16·0

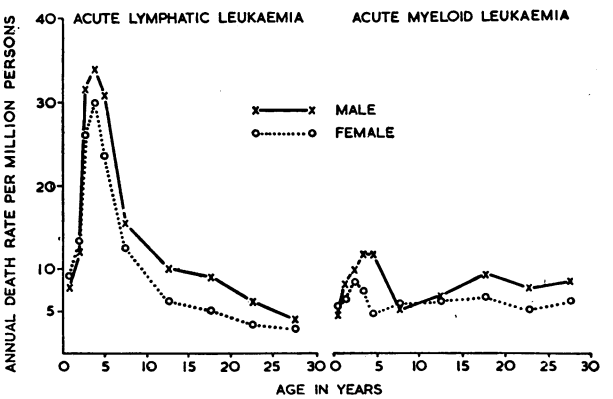

FIG. 2.—Estimated age-specific death-rates from acute lymphatic leukaemia and acute myeloid leukaemia under the age of 30 years by sex in England and Wales, 1945–59.

Trends in Leukaemia Mortality with Time

Leukaemia death-rates for England and Wales by sex and in five-year age-groups have been published for quinquennia from 1911–16 to 1951–5 by McKenzie, Case, and Pearson (1957). Similar figures for the three quinquennia 1945–50 to 1955–9 are shown in Tables II and III. The trends in the mortality with time for the separate five-year age-groups are illustrated in Fig. 3. The rates are shown on a logarithmic scale, so as to facilitate comparison of the relative rates of increase. There is no obvious difference in the trends, save that the rate of increase has been somewhat greater in the youngest age-groups. The average rate of increase over the 50 years examined was approximately 4.5% per annum at ages under 10 years and decreased to less than 4% at ages 20–29 years. In two age-groups (0–4 years and 15–19 years) there was no increase during the last 10 years.

*The estimated rates for the chronic leukaemias at age 15 to 29 years differ slightly from those published previously (Court Brown and Doll, 1959) because the method of allocating the deaths attributed to leukaemia without specification of the clinical type was different. The previous study was concerned with a larger area range, and at older ages the present method would have been inappropriate. At ages 15–29 years, however, the difference in the results obtained by the two methods is trivial and, for the purpose of the present study, can be ignored.

The explanation of these changes is likely to be complex. To a large extent they may be due to improvements in case-finding and to more accurate certification of causes of death, particularly in the early part of the period examined. Stewart (1961) has pointed out that the introduction of sulphonamides and of antibiotics will have allowed a number of cases to become recognizable clinically, whereas previously pneumonia or some other infection might have been fatal during the early and unrecognized stage of the disease. More recently there have been improvements in therapy which may have produced remissions of such length that the relative values of the age-specific mortality rates at the youngest ages have been changed. In our opinion, however, it is difficult to account for the continued increase in mortality at young adult ages by these factors alone, and it seems probable that some of the increase has been due to a true increase in the incidence of the condition.

Trends in the mortality from the various types of leukaemia during the period 1945 to 1959 are shown in Tables II and III. Some increase has occurred in the mortality attributable to both acute lymphatic leukaemia and acute myeloid leukaemia ; but this has been largely at the expense of the other and unspecified leukaemias. Changes in the average annual mortality rate for both sexes taken together for ages 0–14 years and for ages 15–29 years are shown in Table IV. In the younger

TABLE II.—*Male Mortality from Leukaemia in England and Wales, 1945–59, Divided by Age (0 to 29 Years), Type of Leukaemia and Period*

Period	Age (Years)	Annual Death Rate per Million Males from: Acute Lymphatic	Acute Myeloid	Other and Unspecified Acute	Chronic Lymphatic	Chronic Myeloid	Total Leukaemia
1945–9	0	8·8	4·1	15·5	0·5	0·0	28·9
	1	13·8	5·8	15·4	0·5	0·0	35·6
	2	26·7	7·8	18·4	2·0	2·0	56·8
	3	31·0	8·5	21·8	3·0	0·0	64·3
	4	27·2	8·2	16·5	1·3	0·0	53·2
	0–4	20·9	6·8	17·4	1·4	0·4	46·9
	5–9	11·5	4·7	9·3	0·3	0·1	25·8
	10–14	9·3	4·1	7·1	0·3	0·1	20·9
	15–19	8·4	7·1	7·7	0·3	0·5	24·0
	20–24	4·0	5·0	6·3	0·4	1·0	16·8
	25–29	3·3	5·0	4·6	0·1	1·3	14·3
1950–4	0	9·9	6·4	9·9	0·0	0·6	26·7
	1	10·9	8·6	10·9	0·0	0·6	31·0
	2	37·4	12·3	13·4	0·6	0·6	64·1
	3	33·2	13·7	20·0	2·1	0·5	69·6
	4	28·6	10·6	16·4	0·0	0·5	56·1
	0–4	24·3	10·4	14·3	0·6	0·6	50·1
	5–9	16·2	5·2	10·1	0·0	0·5	32·0
	10–14	10·1	9·7	4·9	0·4	0·1	25·3
	15–19	9·4	11·7	5·7	0·0	0·3	27·0
	20–24	7·3	8·3	4·3	0·3	1·0	21·2
	25–29	4·6	9·5	4·8	0·1	1·8	20·8
1955–9	0	5·0	5·0	7·3	0·0	0·0	17·3
	1	12·7	10·4	6·9	0·0	0·0	29·9
	2	30·5	9·4	11·1	0·0	0·0	51·0
	3	36·4	11·9	11·3	1·2	1·8	62·6
	4	37·1	15·6	10·2	0·0	1·2	64·0
	0–4	24·0	10·4	9·3	0·6	0·6	44·5
	5–9	17·7	7·8	9·4	0·9	0·7	36·5
	10–14	10·3	6·8	5·0	0·6	0·9	23·5
	15–19	8·5	9·7	6·4	0·4	0·7	25·7
	20–24	6·9	9·7	5·6	0·3	1·1	23·5
	25–29	3·9	8·8	5·3	0·5	3·1	21·7

TABLE III.—*Female Mortality from Leukaemia in England and Wales, 1945–59, Divided by Age (0 to 29 Years), Type of Leukaemia, and Period*

Period	Age (Years)	Annual Death Rate per Million Females from: Acute Lymphatic	Acute Myeloid	Other and Unspecified Acute	Chronic Lymphatic	Chronic Myeloid	Total Leukaemia
1945–9	0	8·7	4·4	9·2	0·0	0·0	22·3
	1	12·3	4·5	10·6	0·0	0·0	27·3
	2	24·0	5·9	18·1	0·3	0·3	48·6
	3	25·5	3·2	14·7	0·3	1·0	44·7
	4	21·2	1·3	11·9	0·7	0·0	35·1
	0–4	17·9	3·9	12·8	0·2	0·2	35·2
	5–9	9·7	3·7	8·7	0·2	0·2	22·4
	10–14	6·7	4·4	5·0	0·2	0·3	16·6
	15–19	5·1	5·0	6·4	0·0	0·3	16·7
	20–24	4·7	3·9	3·4	0·1	0·6	12·7
	25–29	3·0	4·6	3·6	0·2	1·4	12·9
1950–4	0	9·8	7·3	12·8	0·0	0·0	29·9
	1	12·7	7·8	7·2	0·6	0·0	28·4
	2	28·1	6·4	16·4	1·2	0·6	52·6
	3	27·1	10·0	18·8	0·6	0·6	57·0
	4	24·4	7·2	12·7	0·0	0·0	44·3
	0–4	20·6	7·8	13·7	0·5	0·2	42·8
	5–9	13·0	7·0	8·0	0·1	0·1	28·2
	10–14	5·0	6·8	4·1	0·0	0·3	16·2
	15–19	5·2	8·2	3·5	0·0	0·3	17·1
	20–24	4·6	5·2	3·1	0·1	1·5	14·6
	25–29	2·9	7·9	3·3	0·3	1·2	15·6
1955–9	0	9·4	5·3	10·6	0·0	0·0	25·4
	1	15·1	6·1	10·9	0·6	1·2	33·9
	2	24·7	13·0	8·6	0·0	0·6	46·9
	3	37·0	8·2	15·0	1·3	0·0	61·4
	4	23·9	5·7	10·1	0·6	0·0	40·2
	0–4	21·8	7·6	11·0	0·5	0·4	41·3
	5–9	14·8	7·6	6·3	0·5	0·4	29·6
	10–14	6·9	8·4	4·1	0·0	0·4	19·8
	15–19	4·5	7·5	4·0	0·0	0·9	16·9
	20–24	3·2	7·4	3·2	0·1	0·4	14·3
	25–29	3·4	9·6	4·0	0·3	2·7	20·0

TABLE IV.—*Mortality from Various Types of Leukaemia, England and Wales, 1945–9 to 1955–9**

Type of Leukaemia	Death Rate per Million Persons per Year: Ages 0–14 Years 1945–9	1950–4	1955–9	Ages 15–29 Years 1945–9	1950–4	1955–9
Acute lymphatic	12·7	14·9	15·9	4·8	5·7	5·1
,, myeloid ..	4·5	7·8	8·1	5·1	8·5	8·8
Other and unspecified acute ..	10·1	9·2	7·5	5·4	4·1	4·8
Chronic lymphatic	0·5	0·3	0·5	0·2	0·1	0·3
,, myeloid	0·2	0·3	0·6	0·9	1·0	1·5
All types ..	28·0	32·5	32·5	16·3	19·4	20·4

* Mean death rates for three 5-year age-groups in each sex.

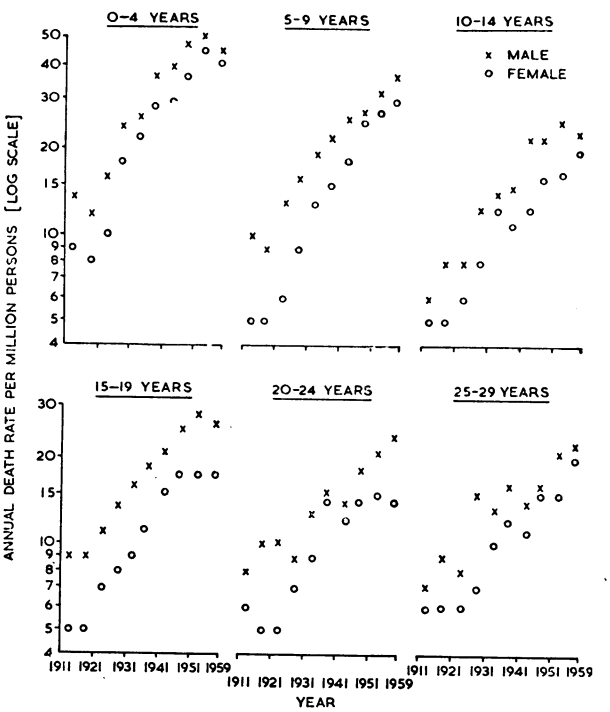

FIG. 3.—Trend in leukaemia mortality with time in England and Wales from 1911–15 to 1955–9 for five-year age-groups from 0–4 years to 25–29 years, by sex.

age-group the changes show that there has been a somewhat greater proportional increase in acute myeloid leukaemia than in acute lymphatic leukaemia, but it would be reasonable to suppose that the increase had affected both types equally and that a greater proportion of the other and unspecified group had been transferred to acute myeloid than to acute lymphatic leukaemia. In the older age-group the position is different. The reduction in the other and unspecified leukaemias is small (5.4 per million to 4.8 per million) and it is smaller than the increase in acute myeloid leukaemia (5.1 per million to 8.8 per million). There is also evidence of an increase in chronic myeloid leukaemia (0.9 per million to 1.5 per million), and it seems likely that at these ages there has been a real increase in the mortality from myeloid leukaemias.

The Childhood Peak

The existence of a peak mortality between 2 and 4 years of age has long been recognized from hospital studies (Cooke, 1942). Mortality data suggest, however, that it has not been present equally at all times nor in all communities. Hewitt (1955) pointed out that the peak became more marked in England and Wales after 1940, and Gilliam and Walter (1958) showed that a similar change occurred among the white population of the U.S.A.; on the other hand no peak was observed among the non-white population.

TABLE V.—*Mortality from Leukaemia in Childhood, England and Wales, 1911–59*

Sex	Period	Annual Death Rate per Million Aged:				
		< 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.
Male	1911–15	9·8	16·5	17·9	14·3	10·6
	1916–20	11·5	14·2	10·7	14·2	11·6
	1921–30	16·4	15·4	20·7	23·4	22·7
	1931–5	19·0	19·2	34·5	28·8	30·5
	1936–9	27·6	36·2	35·3	42·8	39·0
	1940–4	28·1	24·1	49·6	59·5	32·3
	1945–9	28·9	35·6	56·8	64·3	53·2
	1950–4	26·7	31·0	64·0	69·6	56·1
	1955–9	17·3	29·9	51·0	62·6	64·0
Female	1911–15	10·0	12·5	6·4	8·5	5·3
	1916–20	10·0	8·7	9·6	8·0	5·0
	1921–30	12·1	12·0	16·4	15·2	13·5
	1931–5	20·4	24·6	23·6	24·7	16·9
	1936–9	30·5	17·9	32·9	23·0	19·2
	1940–4	27·4	30·7	30·1	36·2	20·7
	1945–9	22·3	27·3	48·6	44·7	35·1
	1950–4	29·9	28·4	52·6	57·0	44·3
	1955–9	25·4	33·9	46·9	61·4	40·2

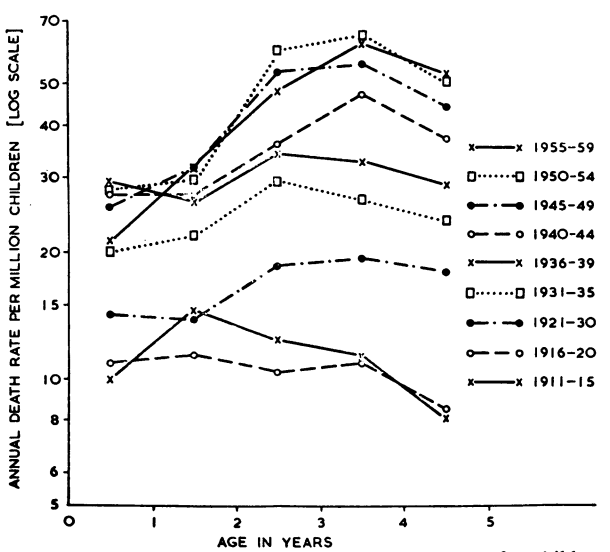

FIG. 4.—Leukaemia mortality at ages 0 to 4 years for children in England and Wales between 1911–15 and 1955–9; mean values for both sexes.

Table V shows the mortality rates for children in England and Wales from 1911 to 1959 for single years of age from 0 to 4 years. Data before 1945 were extracted from the Registrar-General's *Annual Statistical Reviews of England and Wales* and from part III of the *Decennial Supplement for 1921–30* (Registrar-General, 1952). Before 1940 the figures excluded mortality attributed to aleukaemia, which was then classified with Hodgkin's disease; but the number of deaths attributed to Hodgkin's disease in this age-group is so small that the deficiency must be trivial. The shape of the age-distribution curve at different periods is illustrated in Fig. 4; the mortality rates are shown on a logarithmic scale to facilitate comparison of the relative increases at different ages.

From Fig. 4 it is seen that the 2- to 4-year-old peak in childhood mortality was first recorded in 1921–30 and that subsequently there was little change in the pattern of mortality until 1940–4, when the mortality at ages 2 to 4 years again began to rise relative to the mortality at younger ages. As a result, by 1955–9 the mortality at ages 2, 3, and 4 years was approximately double that in the first two years of life.

Among the white population of the U.S.A. the pattern of childhood mortality has been similar (Table VI and Fig. 5). Data are not shown before 1940 because there

TABLE VI.—*Mortality from Leukaemia in Childhood, U.S.A., 1940–58, by Colour*

Population	Sex	Period	Annual Death Rate per Million Aged:				
			< 1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.
White	Male	1940–4	47·1	41·7	64·0	57·6	49·9
		1945–9	44·5	45·0	62·6	73·6	63·6
		1950–4	31·7	39·8	65·5	81·6	69·4
		1955–8	23·4	36·9	56·9	78·5	77·6
	Female	1940–4	44·0	36·9	48·3	47·4	41·5
		1945–9	39·0	35·4	55·0	59·5	47·9
		1950–4	33·1	34·7	57·3	71·6	62·6
		1955–8	25·7	35·8	53·2	61·6	68·4
Non-white	Male	1940–4	19·9	15·2	14·6	13·9	11·7
		1945–9	34·2	26·0	21·9	11·0	20·0
		1950–4	35·0	27·6	28·5	27·7	20·7
		1955–8	15·7	28·0	26·1	24·6	27·3
	Female	1940–4	22·3	20·1	13·5	14·0	9·1
		1945–9	19·9	18·2	10·6	17·8	13·5
		1950–4	26·2	27·1	23·1	18·7	20·1
		1955–8	20·9	21·4	18·5	17·5	20·9

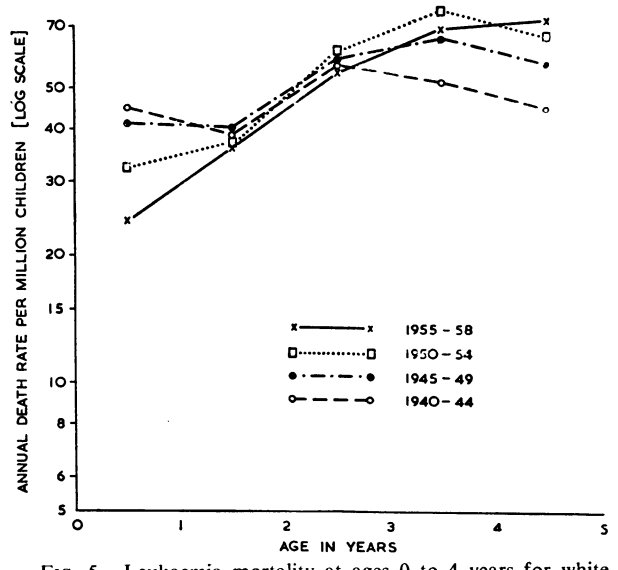

FIG. 5.—Leukaemia mortality at ages 0 to 4 years for white children in the U.S.A. between 1940–4 and 1955–8; mean values for both sexes.

is insufficient information about the size of the population at risk. Since 1940 the death rates have been higher than in Britain but the difference has become less pronounced. In 1940–4 the maximum mortality was recorded at age 2 years; in later periods the peak mortality shifted to age 4 years, and, as in Britain, there was a relative increase in the mortality at ages 2, 3, and 4 years compared with the mortality at younger ages.

The pattern among the non-white population has been strikingly different (Table VI and Fig. 6). At no time has there been any increase in the mean male and female mortality after the second year of life, and in 1940–4 the mortality decreased continuously from the first year onwards. In subsequent periods there has been a relatively greater increase at the older ages, but even in 1955–8 the average mortality at ages 2 to 4 years was very little greater than that recorded at ages 0 and 1 year.

Figures for Japan, provided by the courtesy of Professor Segi, are similar to those for the non-white population of the U.S.A. save that in the most recent period (1955–7) the Japanese mortality has been somewhat higher (Table VII and Fig. 6).

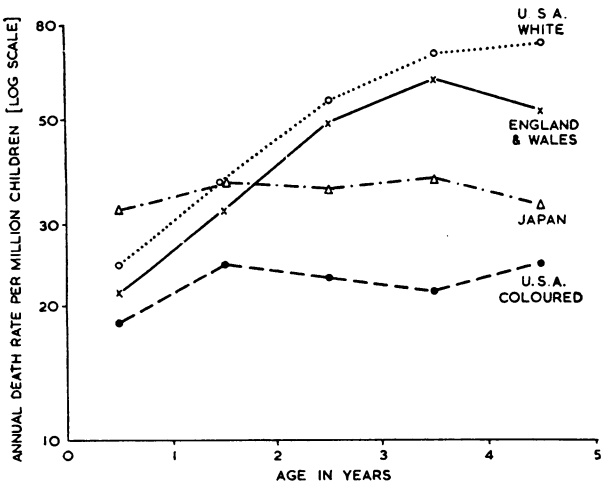

FIG. 6.—Leukaemia mortality at ages 0 to 4 years in England and Wales 1955–9, in the U.S.A. white population and non-white population, 1955–8, and in Japan, 1955–7; mean values for both sexes.

TABLE VII.—*Mortality from Leukaemia in Childhood, Japan, 1940–57*

Sex	Period	Annual Death Rate per Million Aged:				
		<1 yr.	1 yr.	2 yrs.	3 yrs.	4 yrs.
Male	1940–9*	23·6	29·9	18·5	19·1	13·5
	1950–4	26·8	31·2	30·3	27·5	25·6
	1955–7	32·6	43·0	41·5	46·8	36·8
Female	1940–9*	17·7	16·3	15·4	13·7	8·9
	1950–4	23·5	28·1	22·9	17·6	22·7
	1955–7	29·7	29·2	29·1	28·8	29·5

* Data for 1940 and 1947 only.

A comparison of the trends in the relative mortality at ages 2–4 years and 0–1 year is shown in Table VIII. In all four populations there has been a progressive increase in the relative mortality at ages 2–4 years, but there is still no evidence of a peak mortality at these ages in Japan, nor in the non-white population of the U.S.A. In these two populations the distribution of mortality by age in 1950 was similar to that recorded in Britain 30 to 40 years previously.

Burnet (1958) examined the mortality for cohorts of American children born in different years, and concluded that some leukaemogenic factors must have been

TABLE VIII.—*Ratio of the Average Leukaemia Death Rate at Ages 2, 3, and 4 Years to the Average Death Rate at Ages 0 and 1 Year (Male and Female Death Rates Combined); Various Populations, 1911–59*

Period	England and Wales	U.S.A. White Population	U.S.A. Non-white Population	Japan
1911–15	0·86 to 1	—	—	—
1916–20	0·89 ,, 1	—	—	—
1921–30	1·33 ,, 1	—	—	—
1931–5	1·28 ,, 1	—	—	—
1936–9	1·14 ,, 1	—	—	—
1940–4	1·33 ,, 1	1·22 to 1	0·66 to 1	0·77 to 1
1945–9	1·77 ,, 1	1·47 ,, 1	0·64 ,, 1	
1950–4	1·98 ,, 1	1·95 ,, 1	0·80 ,, 1	0·89 ,, 1
1955–9*	2·04 ,, 1	2·11 ,, 1	1·05 ,, 1	1·05 ,, 1

* 1955–8 for the U.S.A., 1955–7 for Japan.

introduced into the U.S.A. about 1942, as the 3-year-old peak in mortality was first evident for children born around that date. As the 3-year-old peak was evident among British children born five years earlier, Doll (1960) concluded that the agent had probably been introduced into Britain before the U.S.A. A more detailed examination of the data, however, throws some doubt on these conclusions.

From Fig. 4 it is evident that there was no sharp change in the age distribution of childhood leukaemia in England and Wales after 1920. Since 1940 the progressive increase in the relative mortality at ages 2–4 years has been shared by other populations, irrespective of the initial age distribution of the disease, and it seems possible that the apparent change in the incidence of the disease may be spurious. Two factors in particular have to be considered. First, improvement in therapy may have resulted in prolongation of life, so that children who are affected at, say, age 2 years may survive temporarily to die a few months later. Secondly, the use of sulphonamides and of antibiotics must have prevented an early death from infection in many cases and so permitted a leukaemic child to survive long enough for the disease to be clinically apparent (Stewart, 1961). There is, however, no obvious similar explanation to account for the change in the pattern of mortality which took place in Britain about 1920, and this may suggest that a new leukaemogenic agent was introduced about this period. The white population of the U.S.A. was presumably exposed at or about the same time, but the negro population of the U.S.A. and the Japanese have either not been exposed or are not susceptible. It is difficult to explain the differences in the age distribution of the disease in these populations by differences in medical care, as there is no consistent difference in the mortality in the first year of life.

The Adolescent Peak

The increase in male mortality at ages 15–19 years illustrated in Fig. 1 has been present in eight out of the nine quinquennia between 1911 and 1955 (McKenzie *et al.*, 1957) and was also present in 1955–9 (Table II). Among girls a similar increase was seen in only four quinquennia. Lee (1961), who first recognized that this peak was not due to random fluctuations, analysed cancer registration data and showed that the irregularity could be entirely accounted for by an increase in a particularly acute type of myeloid leukaemia, in which the duration of symptoms prior to registration was less than two months. That the increase is due principally to a form of acute myeloid leukaemia is also indicated by the mortality data given in Tables II and III and illustrated in Fig. 2.

The occurrence of the peak is not limited to British data, and Lee showed that it was also present in leukaemia mortality figures for the U.S.A. and Canada. Data for 24 countries are given by Segi (1960). In many of these the recorded numbers are too small for useful analysis, and the data shown in Table IX relate only to those populations for which there were more than 30 deaths from leukaemia among males aged 15–19 years during the period 1952–7. In 11 of the 14 populations the male mortality is seen to have been higher at ages 15–19 years than in either of the neighbouring age-groups. It is of interest that the peak is present in Japan and in the non-white population of the U.S.A. despite the absence of a peak in childhood mortality.

Changes in the female mortality are somewhat less marked, but the peak is present in 9 of the 14 populations, and the average increase at ages 15–19 years over the mean for the two neighbouring age-groups is practically the same in each sex (males 126%, females 123%). Some of the increases are substantial (for example, male mortality in Austria and female mortality in Switzerland); but extreme values are likely to occur, due to chance alone, in countries with small populations. There is little correlation between the size of the increase in males and females in individual countries ($r=0.21$), and it is not justifiable to conclude from these figures alone that there is any appreciable geographical variation in the size of the peak.

The latent period for acute leukaemia is of the order of four to eight years when it is induced by irradiation, and, if the duration is the same for other causes, it would appear that the increase at ages 15–19 years was due to an increased stimulus at about the age of 9–13 years.

Sex Ratio

In England and Wales the mortality from leukaemia in the first year of life has been similar in both sexes throughout the period 1931–59. After the second birthday the mortality rate has been consistently higher in boys, and the ratio between the rates for the two sexes has risen to a maximum of about 1.6 to 1 at age 4 years (Table V); at older ages it has fallen and then risen again to approximately the same value at about ages 15–19 years (Tables II and III, and data published by McKenzie *et al.*, 1957). The mortality rates given in Tables VI, VII, and IX show that a similar pattern has occurred in the white and non-white populations of the U.S.A. and in Japan, though in these populations the early peak has been less definite and the age of occurrence irregular. With the exception of the German Federal Republic, the other nine populations, for which age-specific mortality rates are given in Table IX, all show a maximum sex ratio of the order of 1.5–2.0 to 1 between the ages of 15 and 24 years.

Leukaemia in Mongols

The incidence of childhood leukaemia is known to be greater among mongols than among other children (Stewart, Webb, and Hewitt, 1958). In a proportion of cases the fact that mongolism was associated with leukaemia has been recorded on the death certificate, and it has thus been possible to recognize the association of the two conditions in 36 children dying in England and Wales between 1945 and 1959. To these have been added 14 other instances, occurring in the same period, 13 of which were reported through the courtesy of Dr. Stewart and her colleagues. The sex and age distribution of the children at death is shown in Table X.

TABLE X.—*Number of Deaths Attributed to Leukaemia Known to Have Occurred in Mongols, England and Wales,* 1945–59; *Ages* 0–29 *Years, by Sex*

Sex	Period	No. of Deaths Among Mongols Aged (Years):									
		0	1	2	3	4	5–9	10–14	15–19	20–29	All Ages
Male	1945–9	0	2	0	0	0	2	0	0	0	4
	1950–4	0	3	1	1	0	2	0	0	0	7
	1955–9	0	2	4	1	4	1	0	1	0	13
Female	1945–9	0	1	1	1	0	0	0	0	0	3
	1950–4	1	1	2	1	2	0	1	1	0	9
	1955–9	0	2	4	3	2	2	1	0	0	14

As the sex of each child, the age at death, and the date of death are known, it is possible to use the data in Tables II and III to calculate the number of deaths which might have been expected to be attributed to each of the principal types of leukaemia if mongolism was equally associated with all the normal types of childhood leukaemia. On this basis the numbers of deaths attributed to acute and unspecified lymphatic leukaemia, acute and unspecified myeloid leukaemia, other acute and unspecified leukaemia, and chronic leukaemia would have been expected to be 24.7, 11.0, 13.4, and 0.9 respectively. In fact, the numbers of deaths certified as due to these four categories of leukaemia were 22, 14, 14, and 0. In many cases detailed cytological examination would doubtless result in a reclassification of the type of leukaemia. This is, however, presumably also true of leukaemia occurring among children who are not mongols, and unless there is some bias which has resulted in an unusual degree of misclassification among

TABLE IX.—*Mortality from Leukaemia in* 14 *Populations,* 1952–7*; *ages* 0–29 *Years, by Sex*

Sex	Age (Years)	Annual Death Rate per Million Persons in:												
		Canada	United States (White)	United States (Non-white)	Japan	Austra-lia	Austria	Den-mark	England and Wales	France	German Federal Republic	Holland	Scotland	Sweden	Switzer-land
Male	0–4	54·2	56·5	30·8	35·2	58·0	62·0	64·2	49·5	58·8	50·3	52·3	46·1	60·8	58·9
	5–9	34·8	42·3	20·7	23·5	40·1	28·4	40·9	33·4	41·9	36·7	32·1	33·7	37·6	52·7
	10–14	20·2	26·3	18·0	21·4	24·7	20·0	29·9	23·3	31·6	24·9	24·9	26·7	28·9	28·9
	15–19	34·0	28·0	21·8	23·2	21·9	35·8	32·9	28·3	31·1	25·5	36·5	31·5	27·9	32·2
	20–24	21·4	25·1	21·7	20·2	24·6	15·2	27·8	22·6	31·5	20·1	17·8	25·3	22·8	19·6
	25–29	23·3	24·8	21·6	19·3	18·5	25·0	18·4	20·7	26·0	22·9	23·8	12·2	20·0	20·4
Female	0–4	42·5	52·4	23·4	26·8	52·0	41·7	65·9	43·1	49·5	41·3	45·2	32·0	58·1	51·8
	5–9	27·2	33·4	14·0	16·9	26·6	23·6	26·2	27·7	29·9	27·8	29·0	23·5	46·2	32·9
	10–14	21·3	20·7	12·6	15·0	16·4	17·0	21·8	18·8	23·0	15·3	20·6	18·9	22·3	21·8
	15–19	17·9	19·3	12·8	15·8	18·5	20·9	27·4	17·5	24·3	15·7	19·6	21·3	20·4	32·8
	20–24	15·9	14·5	11·5	13·8	12·0	12·6	14·0	14·8	20·1	14·9	18·3	13·5	13·0	10·1
	25–29	15·7	17·3	12·6	14·3	22·5	15·6	13·5	16·8	21·8	16·2	19·8	13·6	25·8	18·3

* Compiled from data published by Segi (1960).

mongols, it would seem reasonable to conclude that the increased risk of acute leukaemia among mongols applies equally to all the principal childhood types.

Genetic Factors

Several families have been reported in which leukaemia has occurred in 2 or more members of the sibship (Steinberg, 1960; Stewart, 1961). Furthermore, cytogenetic studies suggest that trisomy for autosome 21, the typical cytogenetic lesion in mongolism, is associated with the predisposition of mongols towards acute leukaemia. Such an association is strengthened by recent evidence for a specific chromosome abnormality in many cases of chronic myeloid leukaemia, apparently a deletion, thought also to affect autosome 21.

A more complex situation is that reported by Buckton *et al.* (1960), of a family containing three mongol sibs and one apparently normal sib, the latter dying from leukaemia. Cytogenetic studies showed the mother to have a chromosome count of 45, due to the presence of an abnormal translocated chromosome involving autosome 21 and a large acrocentric chromosome thought to be No. 15. It is now known that such translocations may arise either in the ovaries of the mother conceiving the mongol child, or the mother herself may inherit the translocated chromosome. The possibility has also to be considered that the error may originate in, or be transmitted to, the father; although this appears a less likely event. The presence of the translocation in the parental gonad is considered to increase the risk of non-disjunction of autosome 21 during gametogenesis. Thus the one mongol sib of the above family, who was examined, had a count of 46 including the abnormal translocated chromosome and an autosome pair No. 21. The child was effectively trisomic for 21 and, therefore, phenotypically a mongol. It is not impossible that the "normal" sib, who died from leukaemia, had the same karyotype as the mother, and that the development of the leukaemic state is related to this. On the other hand, the association of leukaemia and mongolism in this sibship could have been due to chance, although this would seem to be unlikely.

Mongolism is an example of one type of genetic factor influencing the development of leukaemia. Other genetic factors could, presumably, be demonstrated by a study of identical twins. If, for example, a gene mutation was important in the genesis of childhood leukaemia, it would be expected that the frequency of identical twins, each dying from leukaemia, would be increased among the children dying from leukaemia. We have attempted to test this by studying the frequency of twins among 5,143 children who died from leukaemia in Britain between 1945 and 1959, and also among 282 children dying from aplastic anaemia within the same period. Since approximately 2 in every 250 children are identical twins it would be expected that if concordance is complete and the incidence of leukaemia falls equally on twins and non-twins there ought to have been approximately 20 pairs of identical twins affected (5143/250). In fact there was no example of twins, both of whom were certified as dying from leukaemia. Only one pair of twins was found; one child was certified as dying from leukaemia at the age of 5 years, while the other was certified as having died from aplastic anaemia two months later. Even if both had died of leukaemia—which may not be the case—and the twins were identical, as it is reported they were, the evidence would suggest that the development of leukaemia in identical twins is an uncommon event.

Summary and Conclusions

An analysis has been made of the mortality rates from leukaemia among children and young adults under the age of 30 years in England and Wales during the period 1911–59. Similar data for other countries have been examined over a shorter period.

Data provided by the Registrar-General of England and Wales enabled the deaths which occurred between 1945 and 1959 to be classified according to the clinical and cytological description of the disease. Estimated mortality rates for acute lymphatic leukaemia showed a maximum at age 3 years in both sexes. At subsequent ages the mortality fell to a minimum at ages 25–29 years, with only a slight check at ages 15–19 years. The mortality from acute myeloid leukaemia varied less sharply, but showed two peaks at ages 2–4 years and 15–19 years. The check in the mortality from acute lymphatic leukaemia in late adolescence and the peak in the childhood mortality from acute myeloid leukaemia may be artifacts due to misclassification. The mortality from both types of chronic leukaemia was low throughout the age range studied, but there was evidence of an increase in the mortality from chronic myeloid leukaemia above the age of 20 years.

Between 1911 and 1959 the mortality increased fairly steadily in each five-year age-group and in each sex. The average rate of increase was approximately 4.5% per annum under the age of 10 years and slightly less than 4% per annum at ages 20–29 years. The age-groups 0–4 years and 15–19 years showed no increase in the last 10 years. Part of the increase is likely to be spurious and due to such factors as better case-finding and improvements in the therapy of infections; but it is difficult to account for the continued increase at young adult ages by these factors alone. Data for the last 15 years suggest that there has been a real increase in chronic myeloid leukaemia and in acute myeloid leukaemia over the age of 15 years.

Before 1920 there was no evidence of a childhood peak in the mortality from leukaemia. A peak mortality was present at ages 2–3 years from 1921 to 1939, and since 1940 the peak has become more pronounced. Mortality rates for the white population of the U.S.A. since 1940 have been similar, but at a higher level. Peaks in the childhood mortality have not been observed in the non-white population of the U.S.A. or in Japan.

In England and Wales the male mortality from leukaemia showed a small peak at ages 15–19 years in 9 out of 10 quinquennia between 1911 and 1959; among girls a similar increase was seen less often. An increase in mortality in this age-group has been observed in one or other sex in 13 other populations; in some countries the increase has been more marked in women than in men, and, on average, the proportionate increase over the two neighbouring age-groups has been practically the same in both sexes.

The mortality rate from leukaemia in the first year of life is similar in both sexes. At subsequent ages the male mortality has been higher. In England and Wales the ratio of male to female mortality has been highest at age 4 years and at about ages 15–19 years. In nearly all the other countries studied there is evidence of a high ratio between the ages of 15 and 24 years.

Fifty instances of leukaemia in association with mongolism are known to have occurred in England and Wales between 1945 and 1959. The proportion of deaths attributed to the various types of leukaemia are closely similar to those estimated from the national mortality rates, and it is concluded that the increased risk of acute leukaemia in mongolism affects all the types of the disease commonly observed in childhood.

Examination of the death entries relating to 5,425 children who had died of leukaemia or aplastic anaemia revealed only one example of the occurrence of one or other disease in both members of a pair of identical twins.

We are grateful to the Registrar-General of England and Wales for the extraction of the data; to Professor M. Segi for details of the leukaemia mortality in childhood in Japan; to Dr. Alice Stewart for details of some of the cases of associated mongolism and leukaemia; to Dr. R. A. M. Case for information about the mortality rates for leukaemia in childhood in England and Wales between 1911 and 1930; and to Dr. A. G. Gilliam for information about population estimates in the U.S.A. We are grateful also to Dr. Jean Kennedy, Mrs. V. Peetz, and Mrs. J. Pixner for assistance in the analysis.

REFERENCES

Baikie, A. G., Court Brown, W. M., Buckton, K. E., Harnden, D. G., Jacobs, P. A., and Tough, I. M. (1960). *Nature (Lond.)*, **188**, 1165.
Buckton, K. E., Harnden, D. G., Baikie, A. G., and Woods, G. E. (1961). *Lancet*, **1**, 171.
Burnet, M. (1958). *New Engl. J. Med.*, **259**, 423.
Cooke, J. V. (1942). *J. Amer. med. Ass.*, **119**, 547.
Court Brown, W. M., and Doll, R. (1959). *Brit. med. J.*, **1**, 1063.
Doll, R. (1960). In *Lectures on Haematology*, p. 142, edited by F. G. J. Hayhoe. University Press, Cambridge.
Gilliam, A. G., and Walter, W. A. (1958). *Publ. Hlth Rep. (Wash.)*, **73**, 773.
Hewitt, D. (1955). *Brit. J. prev. soc. Med.*, **9**, 81.
Lee, J. (1961). *Lancet*. In press.
McKenzie, A., Case, R. A. M., and Pearson, J. T. (1957). *Cancer Statistics for England and Wales, 1901–1955: Studies on Medical and Population Subjects*, No. 13. General Register Office. H.M.S.O., London.
MacMahon, B., and Clark, D. (1956). *Blood*, **11**, 871.
Nowell, P. C., and Hungerford, D. A. (1960). *Science*, **132**, 1497.
Registrar-General (1952). *Decennial Supplement, England and Wales, 1931*, Part III. H.M.S.O., London.
Segi, M. (1960). "Cancer Mortality for Selected Sites in 24 Countries (1950–1957)." Department of Public Health, Tohoku University School of Medicine, Sendai, Japan.
Steinberg, A. G. (1961). *Cancer*, **13**, 985.
Stewart, A. (1961). *Brit. med. J.*, **1**, 452.
—— Webb, J., and Hewitt, D. (1958). Ibid., **1**, 1495.
Wells, R., and Lau, K. S. (1960). Ibid., **1**, 759.

"The late Dr. Robert Scot Skirving, a self-styled 'remembrancer' of Australian medicine, spoke of Joseph Bancroft [1836–94] with reverence and admiration. 'There seemed to be nothing in the friendly, untidy town that was Brisbane,' he said, 'that Bancroft was not connected with in some way or other. He knew a lot, and always made it his job to be helpful. He was consulted by everyone in the place, from the Government down. He was just the man for a new country.' The final observation of this wise and critical physician is especially revealing of the characters that brought esteem to Bancroft in his day, and raised the Bancroft tradition. He was just the man for a new country—this is the sum of all his qualities. It includes his deep knowledge and searching mind, his resourcefulness, his self-reliance, and his untiring industry; it includes the extreme utilitarianism that was his hall-mark, and his widely diversified interests; and it surely includes his dedication to his profession and his scientific aims, his full acceptance of community responsibilities and his leadership in all fields of interest. These are the foundations of the Bancroft tradition—the tradition of a great colonial doctor." (Professor Edward Ford, Bancroft Memorial Lecture, *Med. J. Aust.*, February 4, 1961.)

ACUTE MYELOID LEUKAEMIA IN ADOLESCENTS

BY

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The death-rate from leukaemia is high in young children, and then falls to a minimum in early adult life. In the course of studies on morbidity and mortality in adolescents (Lee, 1961) it was noticed that in males the decline in the leukaemia death-rate during adolescence was interrupted by a transient rise (Fig. 1). This excess mortality is not a new phenomenon, but goes back at least to 1911–15. A study of this phenomenon is now reported.

FIG. 1.—Death-rates from leukaemia in males and females by age. England and Wales, 1950–58 (General Register Office, 1957; 1958).

Method

The General Register Office for England and Wales, the General Registry Office for Scotland, the United States National Office of Vital Statistics, and the Canadian Dominion Bureau of Statistics were asked to provide the number of deaths certified to leukaemia by single years of age, over the range 0–29, for as many calendar years as possible. Figures for 1945–57 in England and Wales, for 1950–58 in Scotland, 1950–57 in the United States, and 1949–58 in Canada, were obtained, together with the corresponding population estimates, through the courtesy of these offices.

Leukaemia is not a common disease, and to obtain adequate numbers the data for the whole of the periods available have been combined. In the analysis of mortality, two-year age-groups were found to be a suitable compromise between single years of age, which resulted in too great variations due to small numbers, and conventional five-year age-groups, with their possible obscuring of changes limited to short periods of life.

Further data were provided for 1949–57 through the courtesy of the National Cancer Registration Scheme for England and Wales. A substantial and growing proportion of the cases of malignant disease are reported to this registration scheme, but during these years the number of cases of leukaemia reported in persons aged 15–19 was only about 40% of the deaths certified to leukaemia in England and Wales. Thus division by five-year age groups was the smallest that could usefully be made of these data. Much more information was available about these cases than can be derived from the